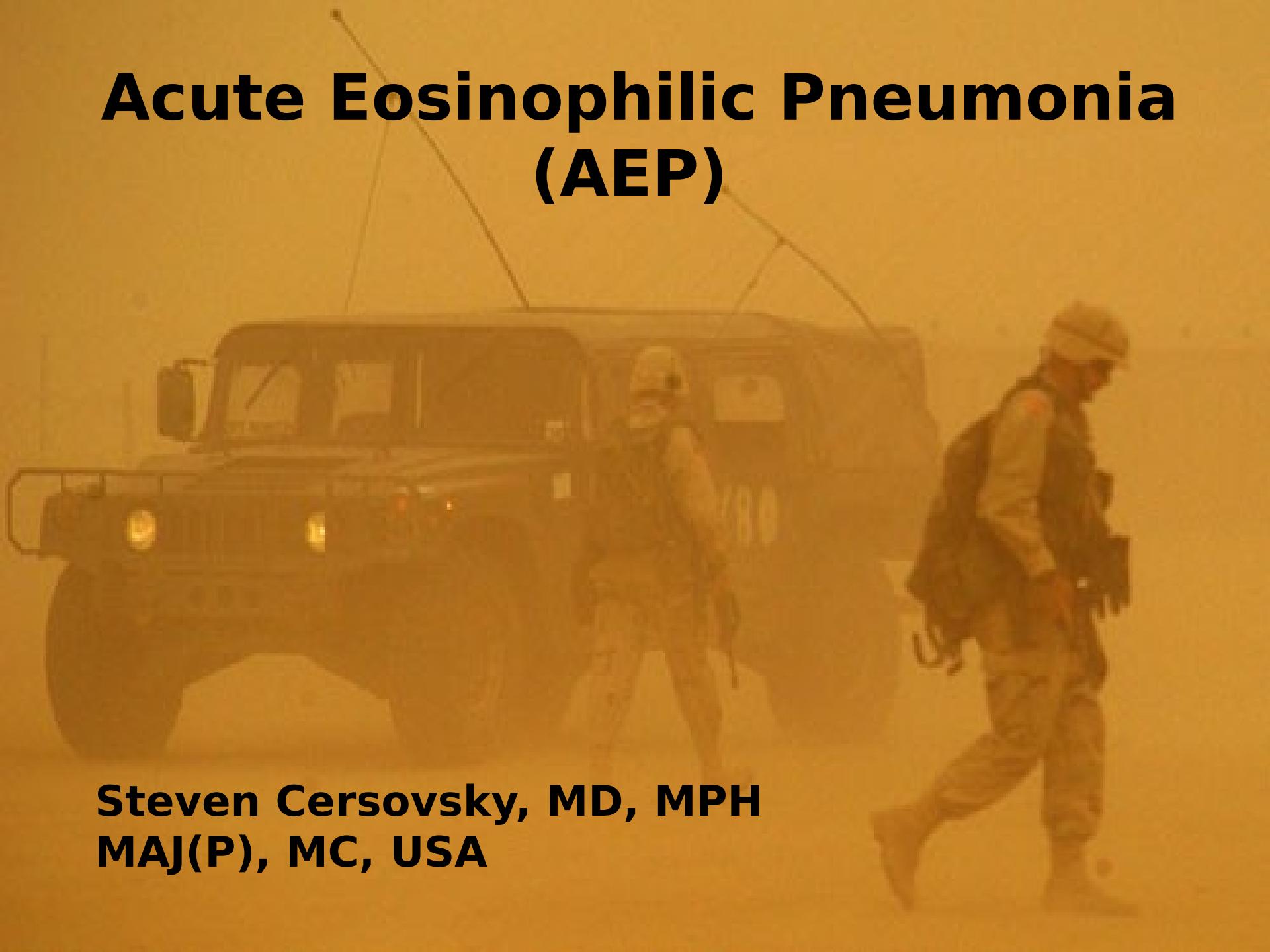


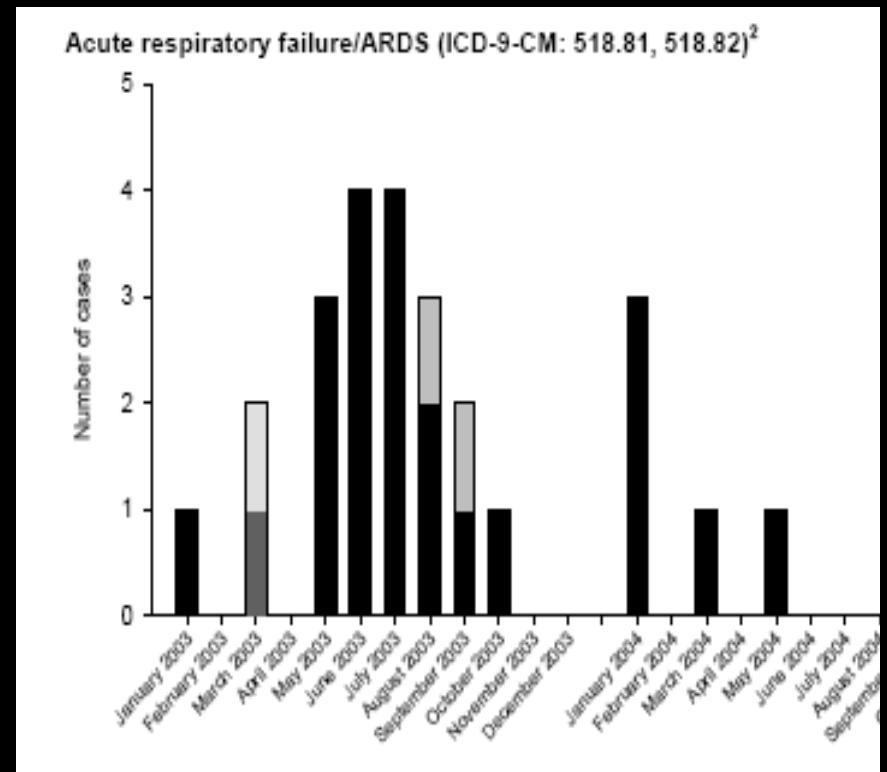
Acute Eosinophilic Pneumonia (AEP)

A blurry, sepia-toned photograph showing a military vehicle, possibly an HMMWV, in a desert setting. Two soldiers are visible; one is standing near the vehicle, and another is walking away from the camera. The image is out of focus and has a warm, monochromatic tone.

**Steven Cersovsky, MD, MPH
MAJ(P), MC, USA**

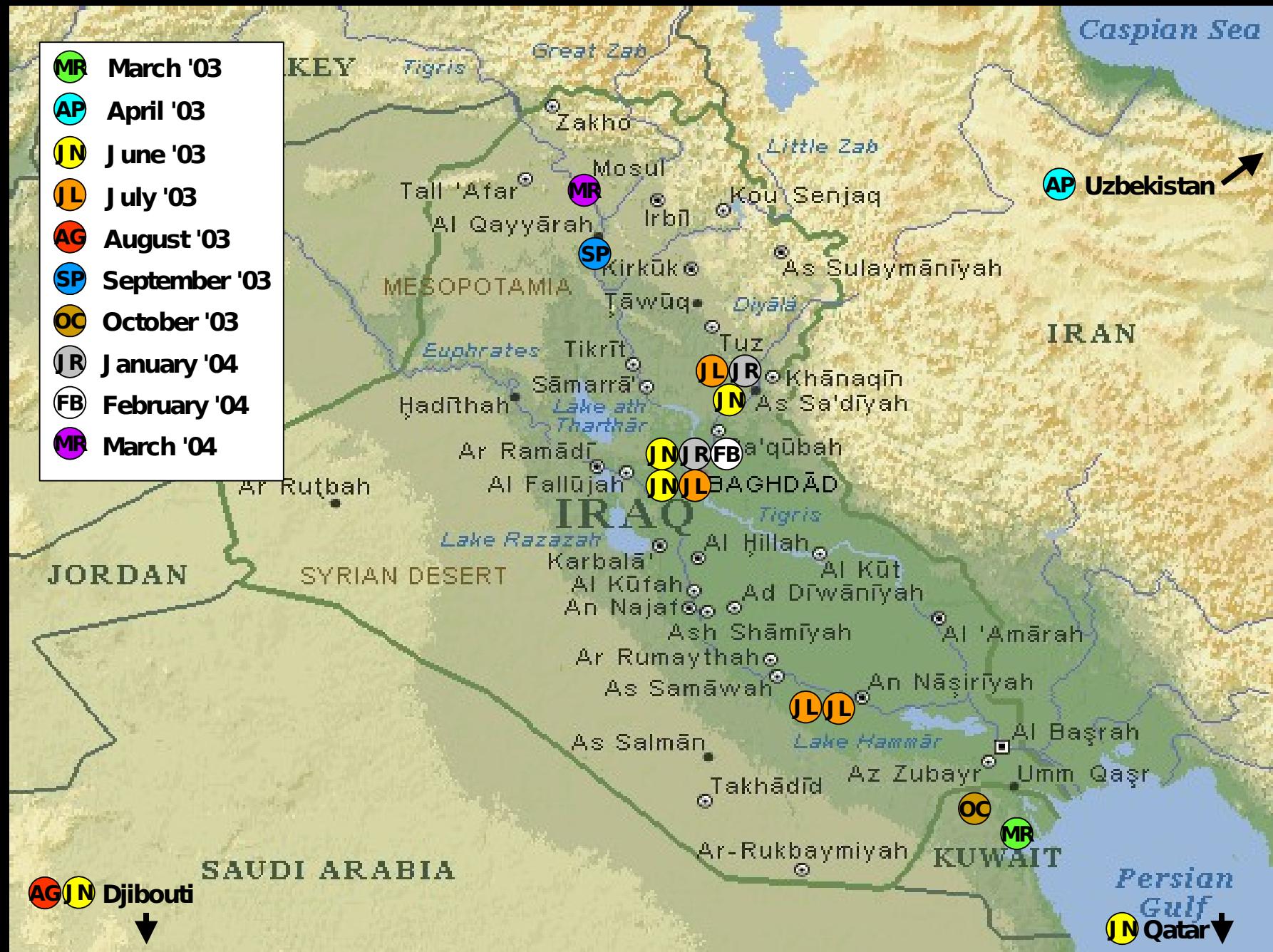
Iraq, 2003

- U.S. Forces
- 19 cases of severe respiratory disease, 2 deaths
- EPICON launched
 - Active case finding
 - Questionnaire to determine risk factors



Methodology

- Questionnaire and database development
- Case finding
- Clinician interviews
- Review of charts, radiographs and laboratory tests
- Case interviews (surrogate interviews for the two deaths)
- Autopsy review
- Follow-up clinical evaluations for 13 severe patients at WRAMC
 - Labs, PFTs, PPD, CXR, pulmonary and allergy evaluations
 - Revised questionnaire
- Tobacco analysis



- General
 - Complete blood count
 - Comprehensive metabolic profile
 - C-reactive protein
 - Erythrocyte sedimentation rate
- Microbiologic Cultures
 - Sputum culture
 - Blood culture
 - Urine culture
 - Stool evaluation for O & P
- Miscellaneous Testing
 - Anti-nuclear antibody
 - Eosinophil cationic protein
 - Hypersensitivity pneumonitis panel
 - Quantitative immunoglobulins
 - Rheumatoid factor
- Serologic Evaluation for Infection
 - Adenovirus Group
 - *Bordetella pertussis*
 - *Chlamydia* spp.
 - Coxsackie B (1-6)
 - *Coxiella burnetii*
 - Hantavirus
 - Histoplasmosis
 - Respiratory Syncytial Virus
 - Influenza A and B
 - *Legionella* (serum and urine)
 - *Mycoplasma pneumoniae*
 - Parainfluenza (1,2,3)
 - Rickettsial Agents
 - SARS
 - *Strongyloides* spp.
 - *Toxocara* spp.
 - *Wuchereria* spp.

Findings

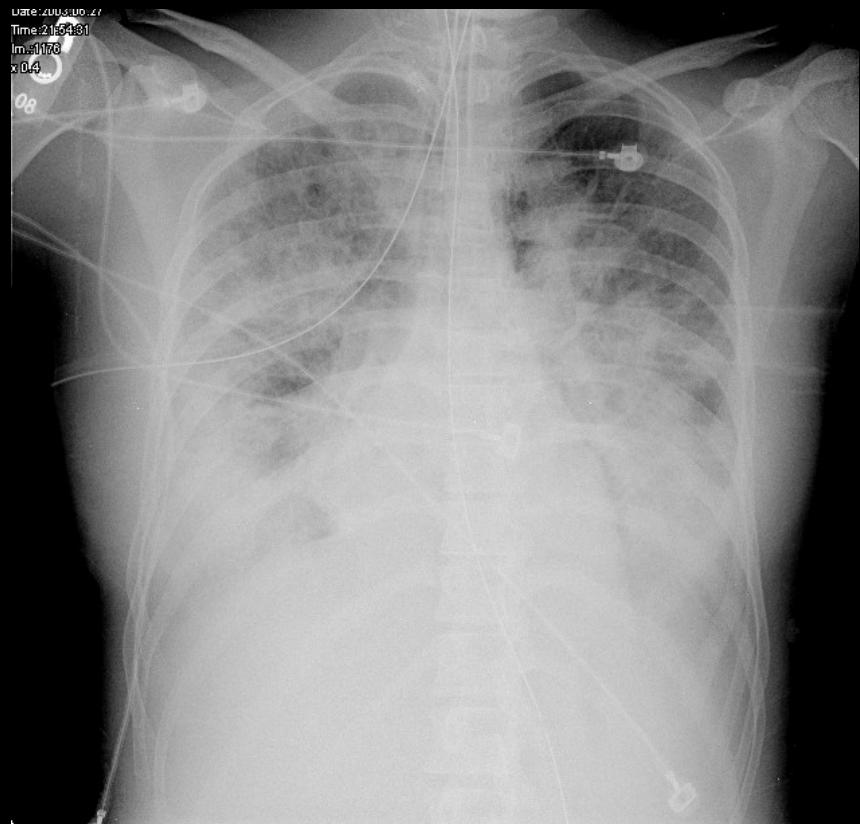
- Higher rate of severe pneumonia compared to Army basic training posts
- Severe pneumonia cases w/o obvious epidemiologic link
 - No relation in person, place or time
 - No common exposures identified
- A variety of possible infectious etiologies for severe pneumonia
- 10 cases with elevated eosinophils
 - New-onset smoking a possible risk factor
 - No common infectious cause, including parasites
 - No specific medication(s) unique to patients with elevated eos
- No evidence of contamination of tobacco products

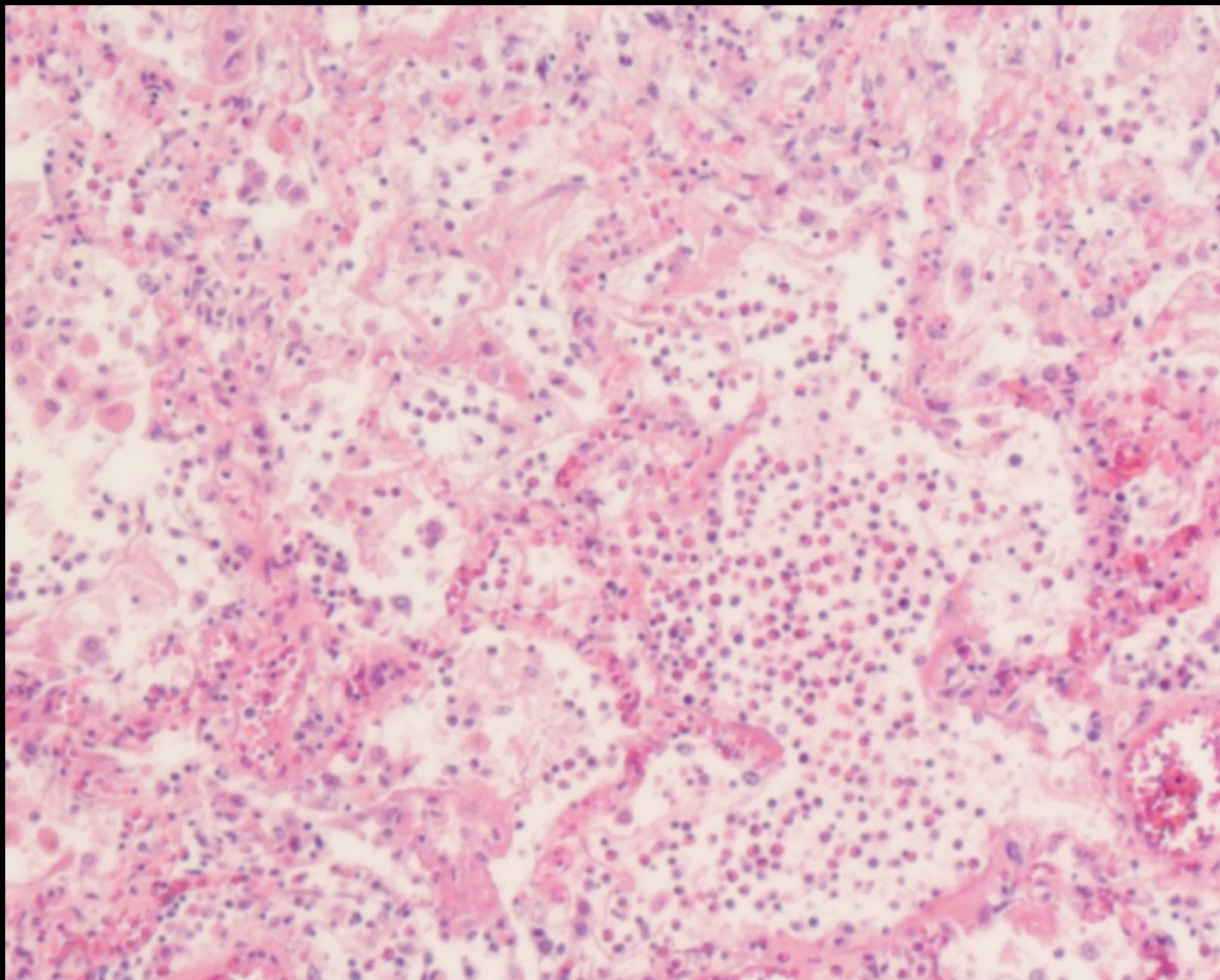
Acute Eosinophilic Pneumonia (AEP)

Acute Eosinophilic Pneumonia (AEP)

Case definition

- Febrile prodrome with acute onset of respiratory symptoms
- Chest radiograph (CXR) with infiltrates
- Definite case: Either lung biopsy with eosinophilic infiltration or BAL with $\geq 5\%$ eosinophils
- Probable case: Never underwent BAL or lung biopsy but developed an unexplained peripheral eosinophilia (total eosinophil count $> 250/\mu\text{L}$ and percentage of eosinophils $\geq 10\%$ of differential cell count)





Demographics

Age

Median

Yrs

22

Range

19-47

Rank

≤ E4

N (%)

24 (86)

E5-E9

3 (11)

Officer

1 (3)

Gender

Male

26 (93)

Female

2 (7)

Race

White

27 (96)

Afr-Am

1 (4)

Demographics

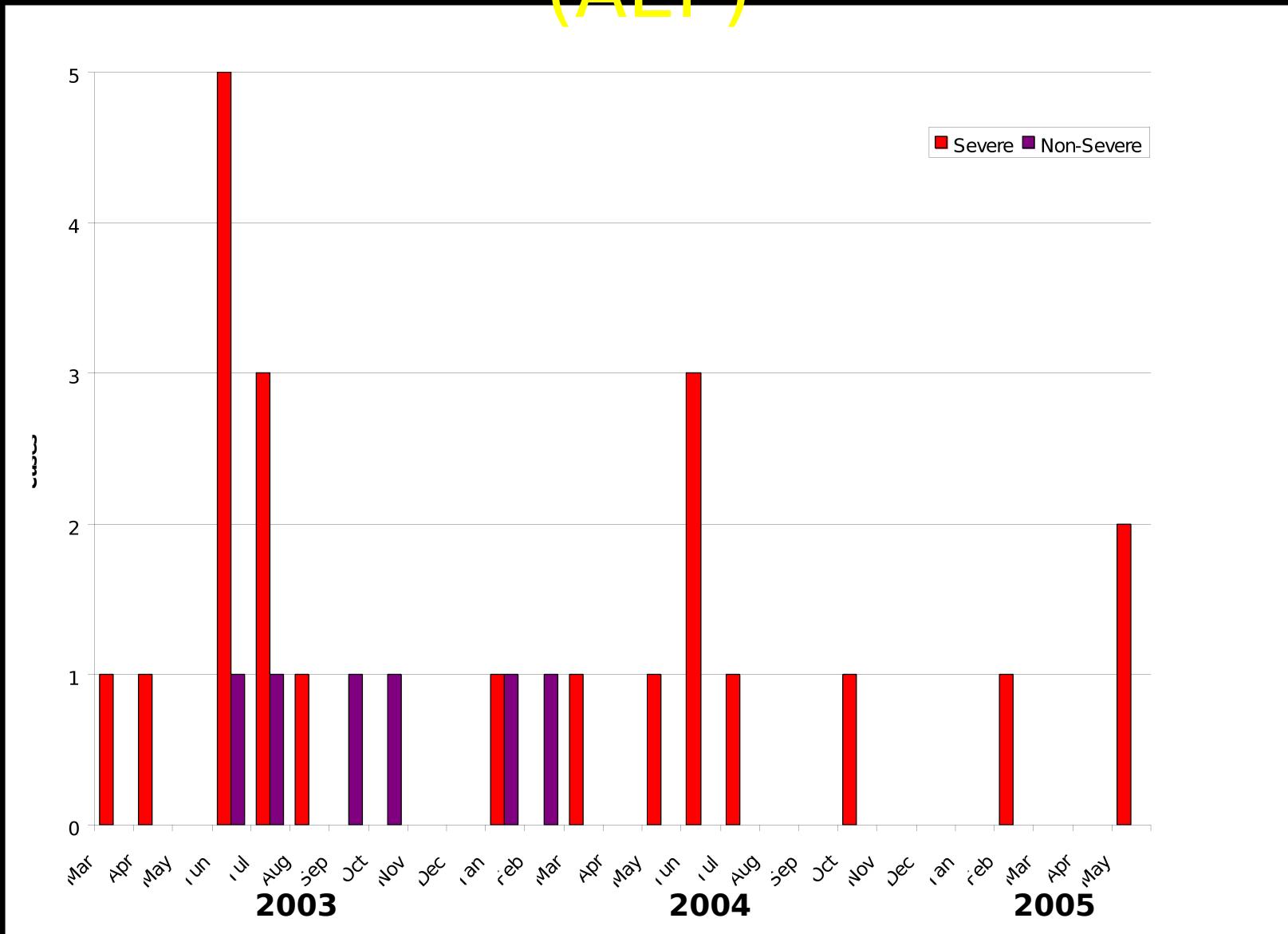
Service

Army	22 (78)
Navy	1 (4)
Marine Corps	5 (18)

Component

Active	15 (54)
Reserves	6 (21)
National Guard	7 (25)

Acute Eosinophilic Pneumonia (AEP)



Smoking history of non-severe^a and severe^b AEP patients during OIF,
March 2003-June 2005

Cigarette smoking	Non-Severe	Sever e	Total
New	4	19	23
Increased quantity	0	3	3
Chronic	2	0	2

^aNon-severe=did not require mechanical ventilation

^bSevere=required mechanical ventilation

Acute Eosinophilic Pneumonia (AEP)

- Etiology undetermined, but evidence suggests one or more inhalational exposures in a predisposed individual. Although not an infection, AEP may present in conjunction with, or as a result of, infectious agents.
- The initiation of tobacco smoking, or a significant increase in the quantity of tobacco smoked, appears to be a major risk factor in the development of AEP.

Acute Eosinophilic Pneumonia (AEP): Treatment

- Cessation of tobacco smoking
- Empiric treatment of CAP
 - 3rd generation cephalosporin (ceftriaxone, cefotaxime)
AND
 - Respiratory tract quinolone (levofloxacin 500-750 mg IV qd) **or** azithromycin (500 mg IV qd)
AND
 - Doxycycline (100 mg IV bid)
- Corticosteroids
 - Solumedrol 80 mg IV q 8 hrs (or equivalent); begin taper over 2-4 weeks as symptoms resolve
- Pressure-control ventilation
- Evacuation from theater

Acute Eosinophilic Pneumonia Among US Military Personnel Deployed in or Near Iraq

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EOSINOPHILIC LUNG DISEASES comprise a variety of processes ranging from Churg-Strauss syndrome to drug reactions.¹ Acute eosinophilic pneumonia (AEP) is a recently described syndrome characterized by a febrile illness, diffuse infiltrates on chest radiograph, and pulmonary eosinophilia.² Generally, patients with AEP present with respiratory failure requiring mechanical ventilation.^{3,4} Clinicians may initially confuse AEP with severe community-acquired pneumonia, acute respiratory distress syndrome (ARDS), or both. It is unclear if less-severe forms of AEP exist.

Histopathologically, lung biopsies in patients with AEP reveal both acute and organizing diffuse alveolar damage with eosinophils filling both the alveolar and interstitial spaces.⁵ Peripheral eosinophilia may be noted in AEP; however, it is often absent at the time of presentation, which complicates efforts at diagnosis and case identification and suggests that the initial insult in this disease occurs in the lungs. Although a num-

Context Acute eosinophilic pneumonia (AEP) is a rare disease of unknown etiology characterized by respiratory failure, radiographic infiltrates, and eosinophilic infiltration of the lung.

Objectives To describe a case series of AEP, illustrate the clinical features of this syndrome, and report the results of an epidemiologic investigation.

Design, Setting, and Participants Epidemiologic investigation of cases of AEP identified both retrospectively and prospectively from March 2003 through March 2004 among US military personnel deployed in or near Iraq. Survivors were offered a follow-up evaluation.

Main Outcome Measure Morbidity and mortality related to AEP.

Results There were 18 cases of AEP identified among 183 000 military personnel deployed in or near Iraq during the study period, yielding an AEP incidence of 9.1 per 100 000 person-years (95% confidence interval, 4.3–13.3). The majority of patients (89%) were men and the median age was 22 (range, 19–47) years. All patients used tobacco, with 78% recently beginning to smoke. All but 1 reported significant exposure to fine airborne sand or dust. Known causes of pulmonary eosinophilia (eg, drug exposures or parasitic disease) were not identified. Epidemiologic investigation revealed no evidence of a common source exposure, temporal or geographic clustering, person-to-person transmission, or an association with recent vaccination. Six patients underwent bronchoalveolar lavage (median eosinophilia of 40.5%). All patients developed peripheral eosinophilia (range, 8%–42%). Mechanical ventilation was required in 67% for a median of 7 (range, 2–16) days. Two soldiers died; the remainder responded to corticosteroids and/or supportive care. Twelve individuals were reevaluated a median of 3 months after diagnosis. At that point, 3 patients reported mild dyspnea and 1 reported wheezing. All patients had finished treatment and had either normal or nearly normal spirometry results. None had recurrent eosinophilia.

Conclusions AEP occurred at an increased rate among this deployed military population and resulted in 2 deaths. Failure to consider AEP in the differential diagnosis of respiratory failure in military personnel can result in missing this syndrome and possibly death. The etiology of AEP remains unclear, but the association with new-onset smoking suggests a possible link.

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Diseases and Immunology (Dr Ockenhouse) and Preventive Medicine (Dr Smoak), Walter Reed Army Institute of Research, Silver Spring, Md. Corresponding Author: Andrew F. Shorr, MD, MPH, Pulmonary, Critical Care, & Sleep Medicine Service, Walter Reed Army Medical Center, 6900 Georgia Ave, Washington, DC 20307 (ashorr@dnmal.com).

Questions?

Epidemiological Consultation (EPICON)

- Late March 2003: 2 patients in ICU at Landstuhl, Germany
- 17 June 2003: First pneumonia death, reports of additional ICU patients at Landstuhl
- 12 July 2003: Second pneumonia death
- 17 July 2003: Tasking from the OTSG
 - Determine if there was an outbreak of severe pneumonia
 - 3 teams deployed
 - Germany (Landstuhl)
 - Iraq
 - United States

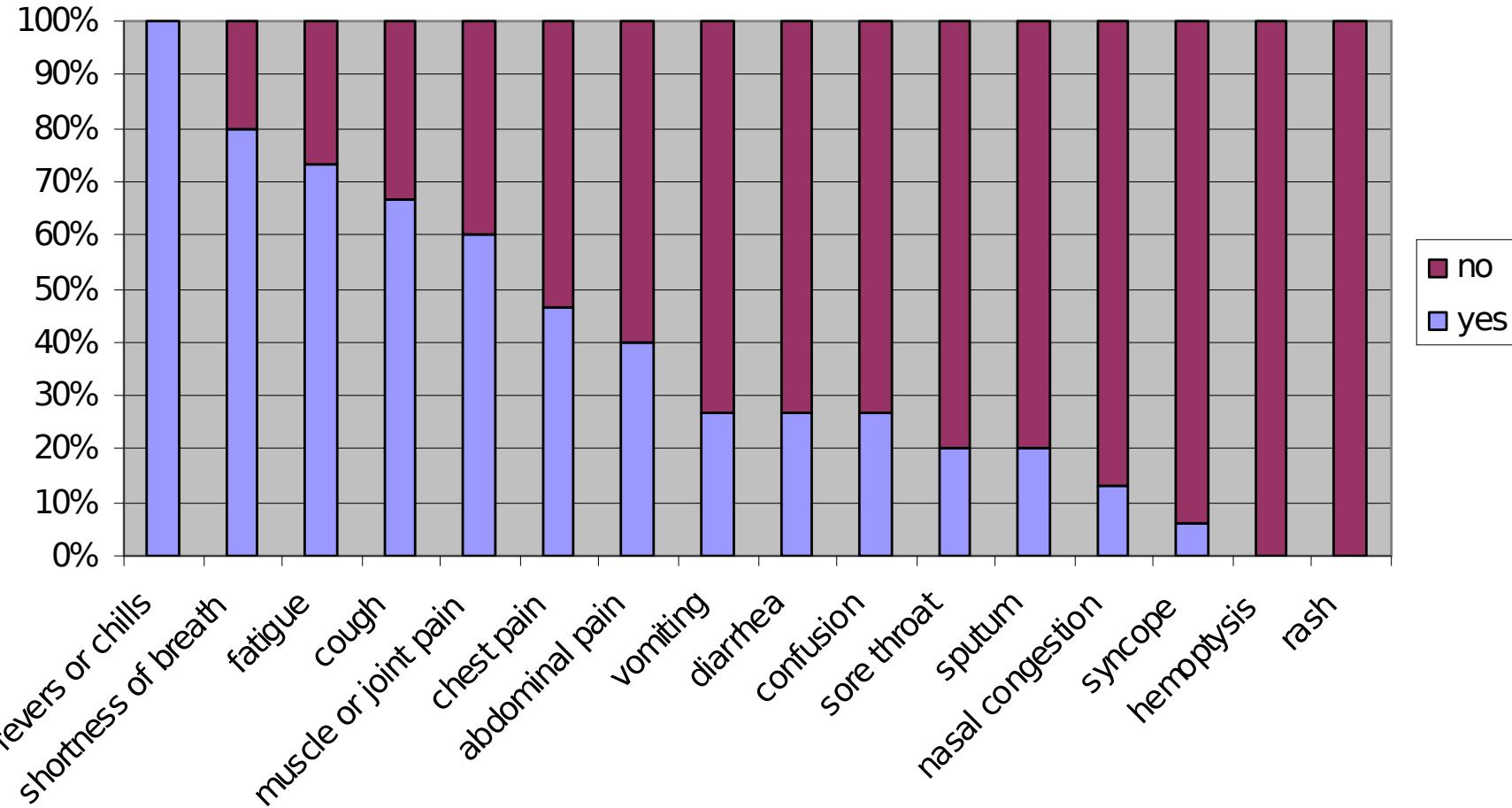
Military Occupation (MOS)

Infantry	3
Armor	2
Artillery	2
Engineer	3
Mechanic	1
Truck driver	2
Fuel/Supply	1
Communication	3
S	
Medical	2

Medical History

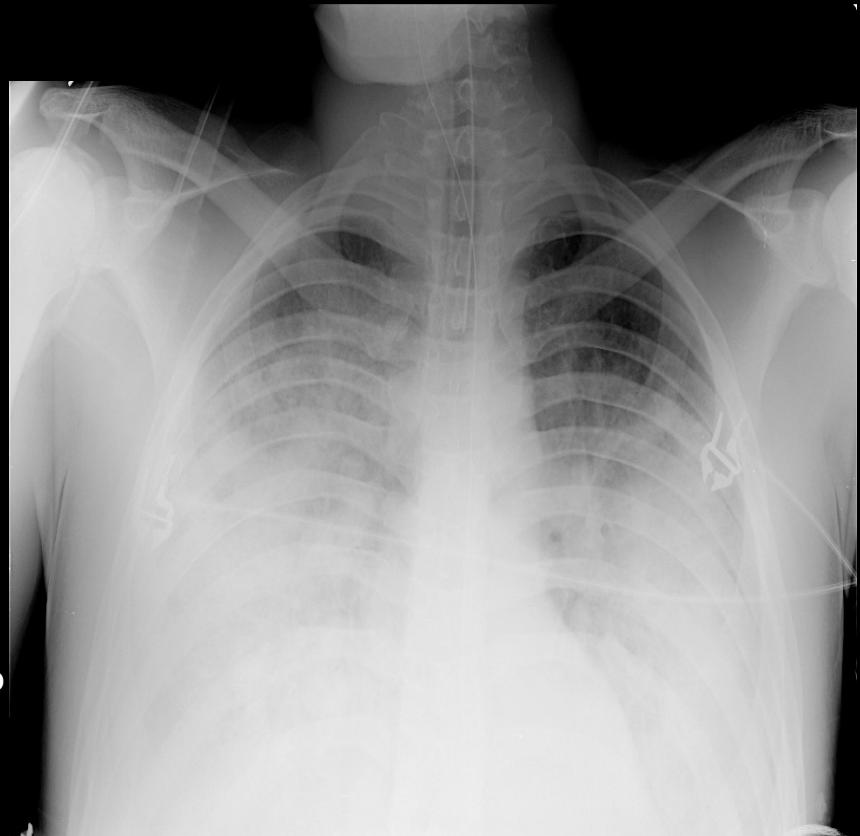
- Generally unremarkable
- No asthma
- Prescription medications
 - Simvastatin (1)
 - Malaria prophylaxis: medication and compliance varied
 - One with latent TB infection; non-compliant with INH
- Over-the-counter medications and supplements
 - Ibuprofen or aspirin as needed (3)
 - Vitamins (3)
 - Creatine (1)
 - OTC stimulant to stay awake (1)

Distribution of Symptoms (n=16)



Overview of Clinical Course

- Symptoms & signs
 - Fever, respiratory distress
 - Elevated WBC count
(Median 13, range 7.3 - 37)
 - CXR w/ bilateral infiltrates
(10 with pleural effusions)
- Antibiotics
 - Levofloxacin 88%
 - Ceftriaxone 65%
 - Doxycycline 59%
 - Imipenem 59%
 - Macrolide 47%
 - Vancomycin 24%
- Steroids given to 8 patients

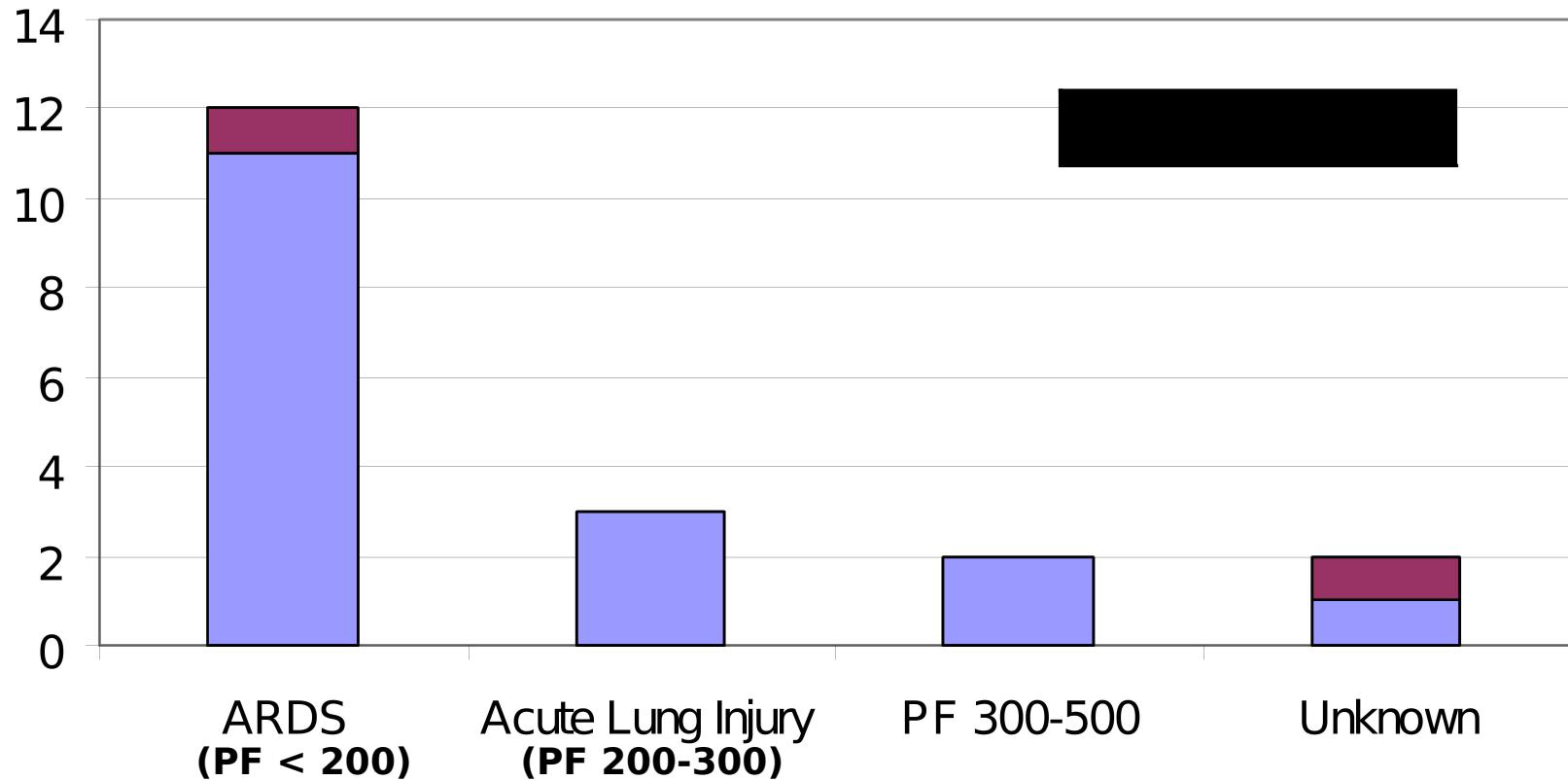


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Pneumonia Severity (PF Ratio)

Distribution of $\text{PaO}_2 / \text{FIO}_2$



Lab Findings

- Culture
 - *Streptococcus pneumoniae* (1) - sputum
 - *Acinetobacter baumanii* (1) - BAL fluid
- Urine antigen
 - *Streptococcus pneumoniae* (1)
- Serology
 - *Coxiella burnetti* (3)
 - *Legionella* spp. (1)
 - Low titers to various respiratory pathogens
 - Fungal & parasitic Abs negative
- Immunology
 - Serum immunoprecipitation to tobacco leaf extracts negative; smoke extracts pending
 - Most patients with evidence of atopy by skin testing

Pneumonia with Elevated Eosinophils

Tissue involvement	
Lung* ± blood	4
Blood only	6
Smoking	
New-onset	9
Chronic	1
Total	10

	Elevated Eosinophils[†]	
	Yes	No
Non-smoker	0	3
New-onset smoker	9	0
Chronic smoker	1*	6

*Bronchoscopic alveolar lavage fluid (3)

Pleural fluid (1)

Tissue from autopsy (1)

[†]Blood absolute count >600 cells/ μ l; pleural fluid and BAL fluid >5%

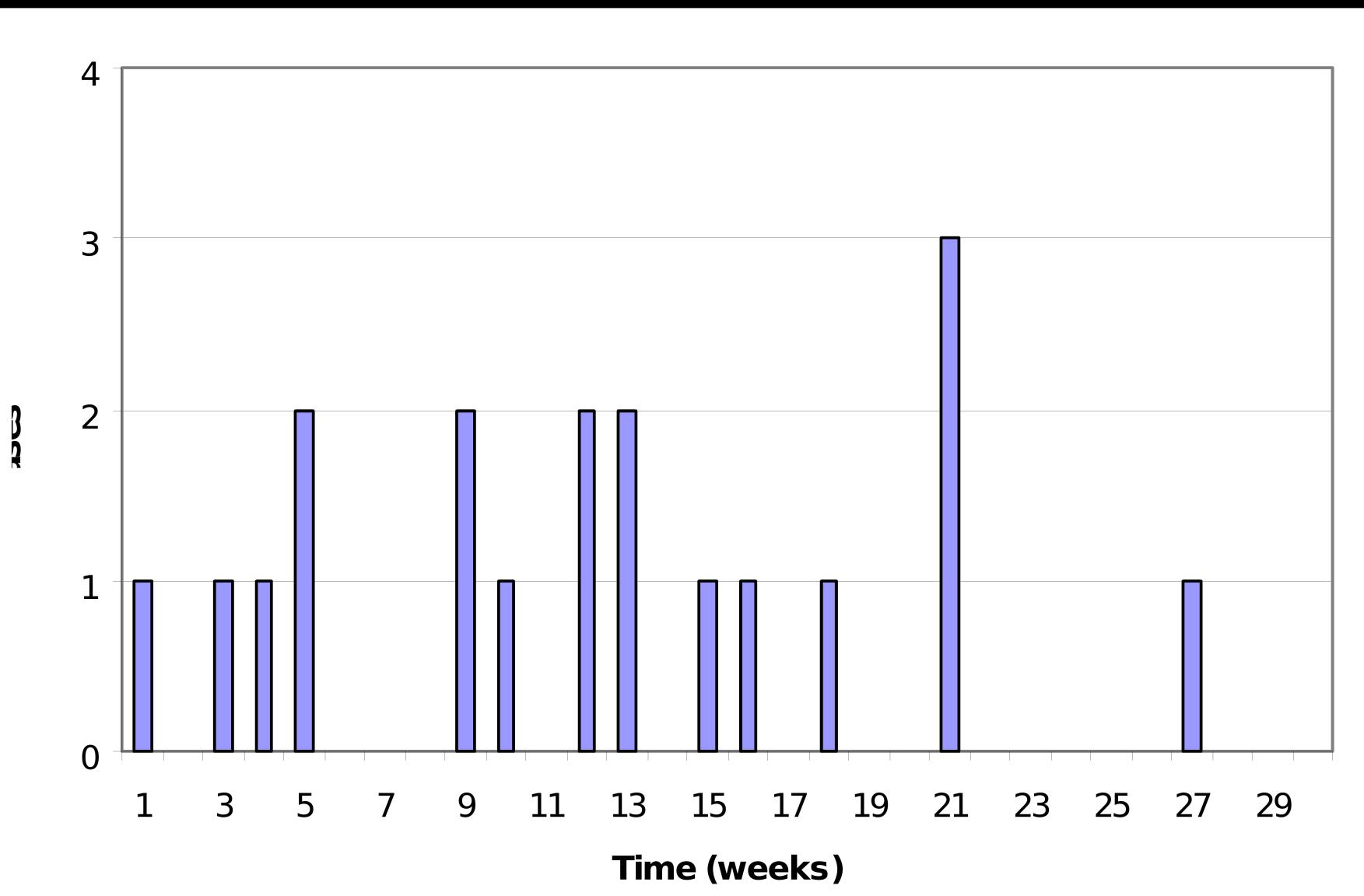
*Unique from the other chronic smokers in that his tobacco use notably increased during deployment

Time from illness onset to elevated eosinophils
Mean = 7.5 days, median = 6.5 days, range 4-14 days

Questionnaire Results

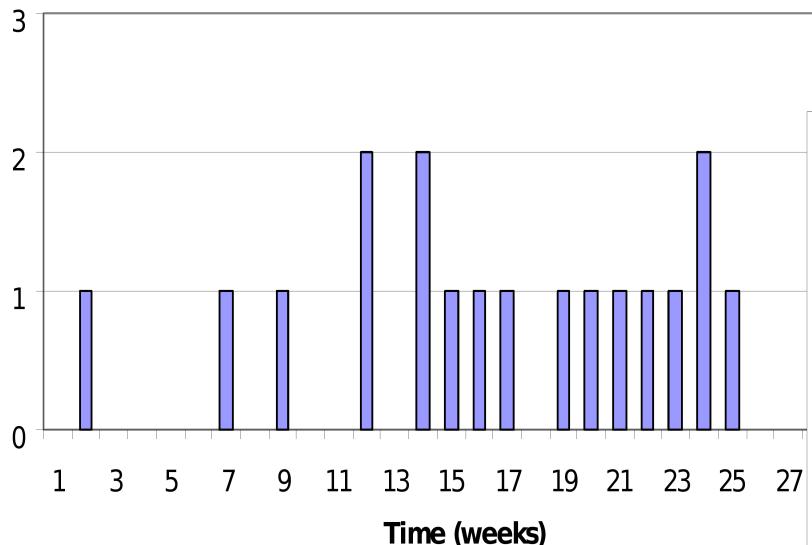
- No common exposures prior to illness
 - Occupational risk factors (daily duties, chemicals, munitions, fuel, etc)
 - Environmental risk factors (water, food, habitat, pollutants, etc)
 - Infectious risk factors (contact with locals, insects, animals, etc)
 - Medications
- Smoking history
 - 16 smokers
 - 7 smoked both foreign and US tobacco
 - 9 began smoking during this deployment

Time from Arrival in Theater to Illness Onset



Smallpox* and Anthrax Immunizations

Time Elapsed from Last Smallpox Immunization to Illness



Time Elapsed from Last Anthrax Immunization to Illness

